Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 35 and 37-42 are pending in the application, with claim 35 being the sole independent claim. Claims 36 and 43-52 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claim 35 is sought to be amended. No new matter is added by way of these amendments. It is believed that the amendments presented above will place the application in condition for allowance and/or in better form for appeal. *See* 37 C.F.R. § 1.116(a). It is respectfully requested that the amendments after final Office Action be entered and considered.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 35-42 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. *See* Office Action, page 2. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *See id.* Applicants respectfully traverse this rejection.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). As discussed below, Applicants submit that a person of ordinary skill in the art would have been able to practice the methods of the present claims without undue experimentation. Applicants also submit that the reasons for the rejection, as set forth in the Office Action, are insufficient to establish a *prima facie* case of non-enablement.

The specification teaches exemplary modes of formulation and administration of antisense oligonucleotides for use in the practice of the claimed methods. *See* specification at page 30, lines 21-27. The specification also teaches various routes of administration that can be used in the context of the present invention such as, *e.g.*, parenteral, subcutaneous, intravenous, intramuscular, intra-peritoneal, transdermal, intrathecal or intracranial. *See* specification at page 31, lines 1-3. Moreover, the specification recites various factors to be

considered in determining the appropriate dosage of antisense oligonucleotides that are administered in the practice of the claimed methods. According to the specification:

> The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. For example, as much as 700 milligrams of antisense oligonucleotide has been administered intravenously to a patient over a course of 10 days (i.e., 0.05 mg/kg/hour) without signs of toxicity (Sterling, "Systemic Antisense Treatment Reported," *Genetic Engineering News 12(12)*:1, 28 (1992)).

Specification at page 31, lines 3-9.

Furthermore, the knowledge in the art regarding the administration of antisense oligonucleotides for therapeutic purposes, in view of the present specification, would have provided additional guidance for the practice of the claimed methods. As noted in Applicants' previous response, there are many examples from the scientific literature that demonstrate successful therapeutic applications of antisense oligonucleotides. *See* Applicants' Amendment and Reply Under 37 C.F.R. § 1.111, filed December 19, 2003 ("the December 19, 2003 response"), at page 12; *see also* Galderisi *et al.*, *J. Cell Physiol. 181*:251-257 (1999) (submitted as Exhibit A with the December 19, 2003 response). These examples would have supplemented the teachings of the present specification and would have provided additional guidance to those of ordinary skill in the art in practicing the currently claimed methods.

In view of the teachings in the specification and the knowledge generally available in the art at the time of the effective filing date of the present application, a person of ordinary

skill would have been able to practice the full scope of methods encompassed by the present claims without undue experimentation.

The Examiner has not set forth a reasonable basis to question the enablement provided for the claimed invention and therefore has not established a *prima facie* case of non-enablement. The Examiner stated that the specification:

> does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment or prevention of disease in general or for the treatment of dementias of Alzheimer's type of neuronal degeneration specifically.

Office Action, page 3. Applicants respectfully disagree. Independent claim 35 specifies that the antisense oligonucleotide used in the practice of the claimed method is complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1. In addition, the specification provides exemplary regions of SEQ ID NO:1 to which the antisense oligonucleotides of the invention may be complementary. *See* specification at page 25, lines 18-24. The specification also notes that antisense oligonucleotides which are non-homologous to pancreatic thread protein (PTP) are preferred. *See* specification at page 26, lines 1-6. A person of ordinary skill in the art, in view of the teachings in the specification and the general knowledge in the art regarding antisense therapies, would have been able to select appropriate nucleotide sequences to effectively interfere with the expression of AD7c-NTP in an animal using the claimed methods. *See also* the December 19, 2003 response at page 10.

The Examiner also stated that "[t]he instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictable [sic] provide for a treatment of disease in general and for the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration in particular." Office Action, page 3. As noted in the December 19, 2003 response (pages 10-11), a person of ordinary skill in the art would recognize that any mode of delivery that brings antisense oligonucleotides into contact with neuronal cells in an animal would be effective in the context of the present invention. In addition, the specification describes various modes of administration that can be used in the practice of the invention. *See* specification at page 30, line 28, through page 31, line 3. The Examiner has not provided evidence or sound scientific reasoning to indicate that any one of these modes of administration would not be expected to work. The Examiner's statement quoted above is insufficient to support the rejection.

In explaining the rejection, the Examiner made several comments relating to the Galderisi reference, which Applicants cited in the December 19, 2003 response. First, the Examiner stated that "it is noted that neither the Galderisi et al reference nor any reference that the examiner is aware of provides evidence of prevention of any disease." Office Action, page 8. Applicants note that the currently presented claims are not directed to the prevention of a disease.

The Examiner has also pointed to various sentences from Galderisi that, when taken out of context, are asserted to support the contention that the use of antisense oligonucleotides is unpredictable. *See* Office action, pages 8-9. For instance, the Examiner quoted the following sentence from the abstract of Galderisi: "The use of antisense

molecules to modify gene expression is variable in its efficacy and reliability, raising objections about their use as therapeutic agents." In the sentences that immediately follow the one quoted by the Examiner, however, Galderisi describes how antisense oligonucleotides have been clinically successful:

> However, preliminary results of several clinical studies demonstrated the safety and to some extent the efficacy of antisense oligodeoxynucleotides (ODNs) in patients with malignant diseases. Clinical response was observed in some patients suffering from ovarian cancer who were treated with antisense targeted against the gene encoding for the protein kinase C-alpha. Some hematological diseases treated with antisense oligos targeted against the bcr/abl and the bcl2 mRNAs have shown promising clinical response. Antisense therapy has been useful in the treatment of cardiovascular disorders such as restenosis after angioplasty, vascular bypass graft occlusion, and transplant coronary vasculopathy. Antisense oligonucleotides also have shown promise as antiviral agents. Several investigators are performing trials with oligonucleotides targeted against the human immunodeficiency virus-1 (HIV-1) and hepatitis viruses. Phosphorothiotate ODNs now have reached phase I and II in clinical trials for the treatment of cancer and viral infections, so far demonstrating an acceptable safety and pharmacokinetic profile for continuing their development. The new drug Vitravene[1], based on a phosphorothioate oligonucleotide designed to inhibit the human cytomegalovirus (CMV), promises that *some substantial successes can be reached with the antisense technique.*

Galderisi, page 251, abstract, (emphasis added). Thus, Galderisi makes it clear that antisense oligonucleotide therapies have been successfully applied in clinical settings.

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[1] Vitravene® is sold by Isis Pharmaceuticals, Inc. The Isis Pharmaceuticals website (http://www.isispharm.com/product_pipeline-P.html, last visited August 25, 2004) lists eleven antisense pharmaceutical products, in addition to Vitravene®, that are in the company's product pipeline. A copy of the Isis antisense product pipeline information, obtained from the website, is submitted herewith as Exhibit A.

In view of the teachings in Galderisi, Applicants maintain their assertions that: (a) the general techniques that were used to produce positive clinical outcomes in the examples mentioned in Galderisi would have been available to persons of ordinary skill in the art at the time of the effective filing date of the present application; (b) the ability of others to successfully apply antisense techniques in the treatment of conditions such as cancer, hematological diseases and cardiovascular disorders strongly suggests that antisense techniques could also have been successfully applied in the treatment of dementias of the Alzheimer's type of neuronal degeneration; and (c) the Examiner has not provided sufficient evidence or sound scientific reasoning to rebut the presumption that Applicants' specification enables the practice of the claimed invention.

Applicants also maintain their position that the references cited at pages 5-7 of the Office Action to support the rejection (*i.e.*, Agrawal (1996), Branch (1998), and Jen and Gewirtz (2000)) do not indicate that the practice of the claimed invention would have required undue experimentation. Indeed, these references describe examples from the art of the successful use of antisense oligonucleotides for the treatment of clinical disorders, and therefore support Applicants' position that the currently claimed invention is fully enabled. *See* the December 19, 2003 response at pages 13-17.

Since the present specification, in view of the teachings in the art, would have enabled a person of ordinary skill to practice the currently claimed methods without undue experimentation, and since no specific scientific evidence or reasoning has been presented to indicate otherwise, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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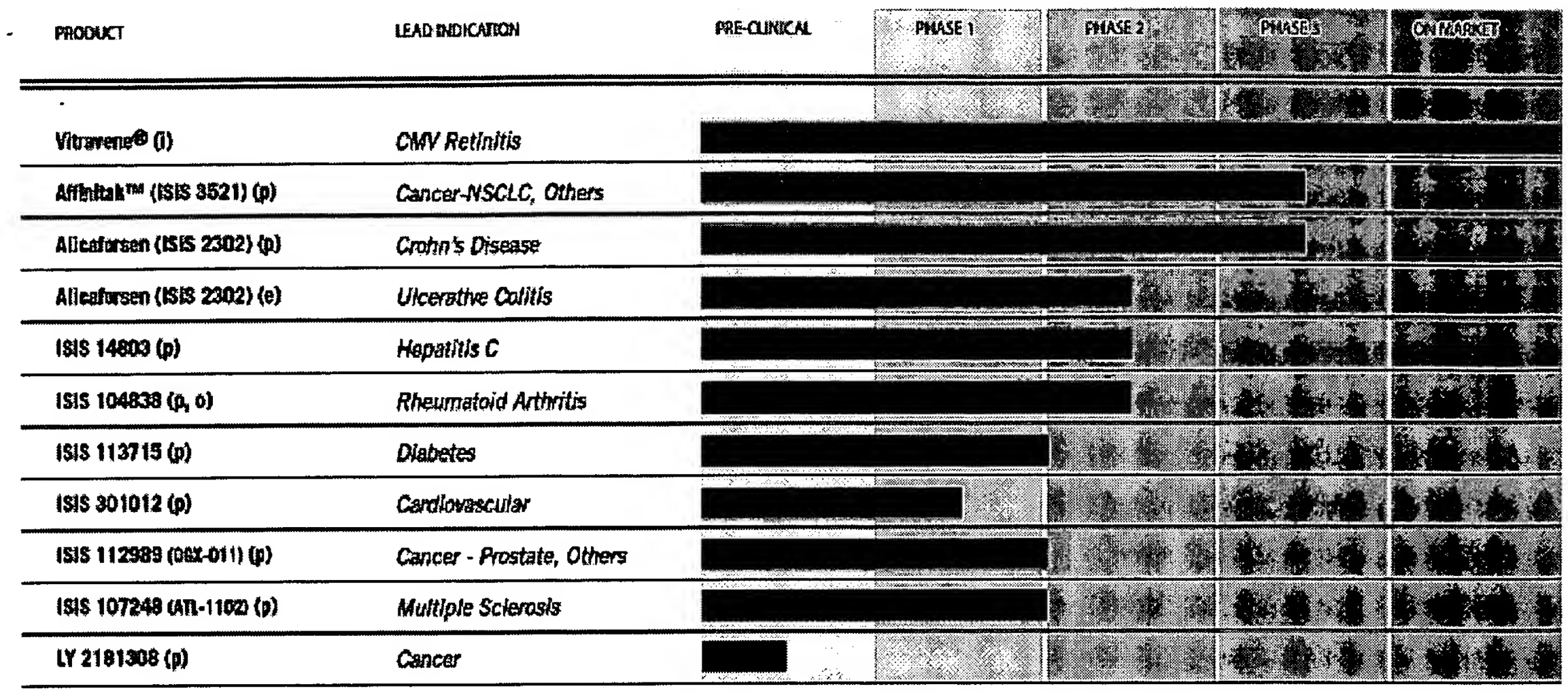

Affinitak™ (formerly LY900003/ISIS 3521)

Affinitak is being developed for the treatment of NSCLC through an alliance between Eli Lilly and Company and Isis. Lilly is conducting a second Phase III trial that is evaluating Affinitak in combination with Gemzar® and cisplatin in patients with NSCLC. Lilly and Isis will make development decisions regarding Affinitak based on the results of this trial, which are expected in the second half of 2004.

Isis announced results of the first Phase III trial of Affinitak in combination with carboplatin and paclitaxel in the 1st quarter of 2003.

Key findings from the study of 616 chemotherapy naïve patients with Stage IIIb or Stage IV non-small cell lung cancer are as follows:

- No difference was observed in a primary log-rank analysis of the overall survival of the two groups (p=0.81). Survival was the primary endpoint of the study. Patients receiving Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel experienced a median survival of 10 months, compared to 9.7 months for patients receiving chemotherapy alone. The median survival of the control group was longer than expected, in light of the fact that 87% of patients had Stage IV disease.

- Using a stratified log-rank statistical analysis that considered predefined variables, including duration of treatment, survival of the Affinitak-treated patients was greater than that of the patients in the control arm. Based on all 616 patients in the study, this result was statistically significant (p=0.048).

- A survival analysis of the 256 patients who completed the prescribed course of chemotherapy showed a median survival of 17.3 months for Affinitak patients versus 14.4 months for patients receiving chemotherapy alone (p=0.054). The prescribed course of therapy was 6 cycles of treatment.

- Additionally, for the 256 patients completing the prescribed course of chemotherapy, results favored the

Affinitak group across multiple secondary endpoints.

- Treatment groups in the trial were comparable with regard to all major prognostic factors. For example, each group had approximately 87% of patients with Stage IV disease and was comparable in terms of types of lung cancer.

- Addition of Affinitak to carboplatin and paclitaxel was well tolerated. There were no increases in severe toxicities or toxicity related deaths in patients receiving Affinitak, compared to those receiving chemotherapy alone. The most common side effects among patients in the study were fatigue and nausea. Patients in the study receiving Affinitak in combination with chemotherapy had a higher rate of moderate thrombocytopenia, nausea and vomiting. Further, because Affinitak is given via continuous intravenous infusion, Affinitak-treated patients had a higher incidence of catheter-related infections.

To read more information about Affinitak, please **click here**.

PKC-alpha: Affinitak's Target

Affinitak is a selective inhibitor to protein kinase c-alpha (PKC-alpha) expression. PKC-alpha is a member of the PKC family, a group of closely related proteins that are involved in a variety of critical cell processes. It is commonly expressed in human cancers and has been found to promote the development, growth and survival of cancer cells. Furthermore, PKC-alpha is associated with resistance to chemotherapy in cancer cells.

NSCLC Facts:

According to the American Cancer Society, lung cancer is the leading cause of cancer death for both men and women. In 2004, an estimated 174,000 new cases of lung cancer are expected to be diagnosed and approximately 157,000 Americans will die due to the disease. More people die of lung cancer than of colon, breast and prostate cancers combined. NSCLC is the most prevalent form of lung cancer, accounting for approximately 80 percent of lung cancer diagnoses in the United States. **(return to pipeline chart)**

Alicaforsen (ISIS 2302) is in late stage development for the treatment of Crohn's disease. An enema formulation of this drug is also being studied in Phase II clinical trials in patients with ulcerative colitis.

Crohn's Disease:

Isis is conducting a Phase III clinical program of alicaforsen in Crohn's disease, with one study taking place in North America and one in Europe and Israel. The studies will evaluate the safety and efficacy of alicaforsen at doses higher than previously studied in controlled trials. Both randomized, double-blinded, placebo-controlled trials have enrolled approximately 150 patients. **(Crohn's clinical trials)**

Isis initiated these Phase III studies based on results from a population pharmacokinetic (PK) analysis of a Phase II study of alicaforsen in patients with Crohn's disease. As reported in May 2001, the results of the analysis showed that the antisense drug may produce clinical disease remissions when patients receive appropriate doses of the drug. Patients receiving the highest dose in the study achieved clinical remission for a median of six months. Alicaforsen was well tolerated in this clinical trial. **(press release)** These data were further supported by results of an open-label, high-dose Phase II clinical trial of alicaforsen, which evaluated doses currently being studied in Phase III trials. **(press release)**

Ulcerative Colitis (UC):

Isis is conducting two Phase II clinical trials of alicaforsen in patients with UC. The purpose of the first study is to compare the safety and efficacy of an enema formulation of alicaforsen to mesalamine enema, a widely used medication for UC. Approximately 170 patients have been enrolled in the randomized, double-masked, active-controlled Phase II study at multiple sites in the U.S.

A second trial is examining the safety and efficacy of different regimens of alicaforsen enema (for example, daily administration compared to treatment every other day) versus placebo for six weeks. Approximately 100 patients have been enrolled at multiple sites throughout the U.S. and Europe.**(UC clinical trials)**

Isis initiated these Phase II studies following the outcome of an initial placebo-controlled, double-blinded European Phase II clinical trial (reported in October 2001). Results from the trial demonstrated that UC patients treated with alicaforsen experienced a dose-dependent reduction in disease activity index score (DAI) and clinical activity index score (CAI), common clinical index scoring systems of the severity of symptoms related to UC. More importantly, the study showed considerable durability of the beneficial response. Alicaforsen and method of administration were well tolerated by patients. **(press release)**

In addition, Isis reported results of a Phase II study of alicaforsen in pouchitis patients at the American College of Gastroenterology (ACG) in 2003. Pouchitis is a UC related condition. The primary endpoint of the trial was improvement in the Pouchitis Disease Activity Index (PDAI), a commonly used 18-point system that evaluates patients' symptom score, endoscopy and histology (each category is scored on a 0-6 scale).

Results from the 12 patients having up to nine months of follow-up are:

• Patients showed improvement in their disease as measured by PDAI and clinical PDAI
- Mean PDAI for all patients in the study decreased from a baseline value of 11.4 to 6.8 after six weeks of treatment. Remission is traditionally defined by a value less than 7. This result was statistically significant (p=0.001).
- Clinical benefit was also observed when evaluating the clinical PDAI (clinical symptom score and endoscopy). Mean clinical PDAI score decreased rapidly from a baseline value of 9.0 to 4.4 (p=0.002) at 6 weeks and was maintained through week 10.

• The most significant improvement was measured by endoscopic analysis of inflamed tissue. Patients experienced a significant improvement in mean endoscopic scores after 6 weeks of treatment (from baseline value of 5.3 to 2.6, p=0.0005) with sustained improvement of up to nine months.

• Alicaforsen enema was well tolerated. **(press release)**

ICAM-1: The Target

Alicaforsen is an antisense inhibitor of ICAM-1, a molecule that plays a key role in a wide range of inflammatory and autoimmune conditions such as Crohn's disease and ulcerative colitis. It is involved in the recruitment and activation of immune cells associated with the inflammatory response in these diseases. ICAM-1 is part of a molecular family (known as Cellular Adhesion Molecules, or CAMs) that can be found on the surface of virtually every cell in the body, including cells that line the inflamed gastrointestinal (GI) tract.

Inflammatory Bowel Diseases (IBD) Facts

According to the Crohn's and Colitis Foundation of America (CCFA) up to one million people have inflammatory bowel disease, evenly split between Crohn's disease and UC. According to the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) a similar number of people in Europe are affected. **(return to pipeline chart)**

ISIS 14803 is being evaluated in patients with drug-resistant chronic hepatitis C virus (HCV). In June 2002, Isis announced the initiation of a Phase II study to assess the benefit of adding ISIS 14803, an antisense inhibitor of HCV viral replication, to standard treatments for hepatitis C virus (HCV). In this trial, ISIS 14803 will be administered to patients who do not achieve an early response to treatment with pegylated interferon and ribavirin.

The company plans to enroll approximately 30 people with genotype 1, drug-resistant HCV in the open-label, dose-escalation study. Along with conventional doses of pegylated interferon and ribavirin, patients will receive ISIS 14803 twice weekly for three months and be followed to determine whether sustained viral responses are achieved. The trial will also assess treatment safety.

ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log dose-dependent reductions in plasma virus levels in patients with HCV, according to final results of a Phase II study reported in October 2003. The majority of the 43 patients participating in the three-month study were HCV genotype 1, the most common and difficult to treat form of HCV, and all but four had been previously treated with interferon.

Two doses and two treatment schedules of ISIS 14803 were evaluated in this trial. All patients initially received 2.5 mg/kg of ISIS 14803 three times a week for two weeks. Patients then received 4 mg/kg or 6 mg/kg of ISIS 14803 either once weekly or twice weekly for 10 weeks by intravenous infusion.

Data highlights are as follows:

-- Five of 17 patients receiving 6 mg/kg of ISIS 14803 twice a week experienced viral titer reductions of 1.0 - 3.8 logs; three patients experienced a greater than 3.0 log reduction.
-- Based on these data, a dose of 6 mg/kg twice weekly will be studied in further clinical trials.
-- In the trial, decreases in viral titers were accompanied by asymptomatic transient increases in alanine aminotransferase (ALT) levels. These data suggest that ALT elevations may correlate with antiviral activity of ISIS 14803.

In an initial one-month Phase I/II study of the antisense drug in patients with chronic hepatitis C virus, escalating doses of ISIS 14803, administered three times a week for one-month by either intravenous infusion or subcutaneous injection, were evaluated. In the trial, five of 28 patients had meaningful viral reductions. Three of 10 patients that received 2 mg/kg of ISIS 14803 experienced 1.3-2.2 log reductions in viral levels. Reductions in viral titers were maintained for more than 40 days. ISIS 14803 was well tolerated in the Phase I/II clinical trial. Adverse events reported were minor. **(press release)**

IRES: The Target

ISIS 14803 targets the IRES/translation region of the hepatitis C virus inducing degradation of the viral RNA and inhibits the translation of viral proteins. These effects have the potential to reduce or halt HCV production.

HCV Facts:

HCV represents a major public health challenge. This potentially deadly disease affects the liver and can eventually cause liver cirrhosis and death. It is estimated that nearly four million people in the United States are infected with HCV. Ten thousand to 12,000 people in the United States are expected to die from this disease each year. There are at least six major genotypes and more than 50 subtypes of HCV. Genotype 1 is the most common genotype in the United States. **(return to pipeline chart)**

ISIS 104838 is being studied in patients with rheumatoid arthritis (RA). It is the first drug based on Isis' proprietary **second-generation chemistry,** called 2'-*O*-methoxyethyl, to enter clinical trials.

Results from Phase I safety studies of intravenous (I.V.) and subcutaneous (S.Q.) delivery of ISIS 104838 demonstrated that antisense drugs based on this improved chemistry offer patients a more convenient dosing schedule, as well as safety advantages. The study also demonstrated substantial improvement in potency and local tolerability compared to first-generation antisense drugs.

Rheumatoid Arthritis

As announced in January 2004, ISIS 104838 produced a significant disease response in patients with rheumatoid arthritis (RA). In the randomized, placebo-controlled trial, 157 evaluable RA patients received subcutaneous injections of either placebo or one of three dose regimens of 200 mg of ISIS 104838: every other week, once weekly or twice weekly. Patients receiving the once- and twice- weekly doses experienced similar responses to treatment, with 41% of evaluable patients achieving a 20% decrease in disease activity. In comparison, 23% of placebo-treated patients achieved a 20% decrease (p=0.05). Response to ISIS 104838 treatment was measured by the American College of Rheumatology (ACR 20) response criteria, a widely used index of RA severity. **(press release)**

These Phase II results add to Isis' strong portfolio of data demonstrating activity of ISIS 104838. Another component of this data package is the Phase II biomarker study which evaluated the biological effect of TNF-alpha inhibition by ISIS 104838 in 20 RA patients over a four-week treatment period. As reported in 2003, ISIS 104838 accumulated in synovial tissue in a dose-dependent manner, reducing TNF-alpha mRNA levels in patients with RA who received 300 mg of the second-generation antisense drug. The synovium, the lining surrounding joints, is inflamed in patients with RA. **(press release)**

Oral Formulations Program

The company is accelerating development of the oral formulation of ISIS 104838 for the treatment of RA. Isis plans to initiate a Phase 2 trial comparing the oral and subcutaneous formulations of ISIS 104838 in patients with RA. In the planned study, which will be conducted outside the U.S., ISIS 104838 will be dosed in combination with methotrexate, a commonly used treatment for RA. Isis expects to initiate this trial in mid-2005.

In November 2002, Isis announced seminal results from a Phase I study in healthy volunteers demonstrating for the first time that solid doses of antisense drugs can be delivered orally. A proprietary capsule formulation of ISIS 104838 achieved drug plasma concentrations sufficient to support further clinical development. Additional Phase I trials in 2003 will further refine the formulation. Based on these data, Isis will select a lead oral formulation and dose schedule that it will further optimize and advance into Phase II clinical trials. **(press release)**

TNF-alpha: The Target

ISIS 104838's target, TNF-alpha, is a naturally occurring cytokine that is an immune system protein responsible for contributing to the activity and progression of many inflammatory diseases. High blood concentrations of TNF-alpha have been observed in patients with RA, Crohn's disease, multiple sclerosis, sarcoidosis, acute liver failure, transplant rejection, congestive heart failure, RA and various skin conditions, including psoriasis.

In RA, TNF-alpha is known to be a major mediator of joint pathology as it stimulates bone and cartilage resorption and drives inflammation. In psoriasis, TNF-alpha contributes to the activity of both skin disease and psoriatic arthritis. In Crohn's disease, TNF-alpha inhibition has been shown to close fistula and decrease disease activity.

RA Facts:

According to the Arthritis Foundation, RA affects 2.1 million Americans, predominately women. RA is a systemic disease that affects the entire body and is one of the most common forms of arthritis. RA is characterized by the inflammation of the membrane lining in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and causes damage to bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

OGX-011 (ISIS 112989)

is an anti-cancer antisense drug, which inhibits clusterin. OGX-011 is currently in Phase I/II development for patients with prostate cancer and other solid tumors.

OncoGenex Technologies, Inc, based in Canada, announced results in June 2004 of a study evaluating OGX-011 as a single agent in patients with high-risk prostate cancer. The Phase I study showed that once weekly intravenous administration of OGX-011 is well tolerated, achieves excellent drug concentration in target tissue, and produces a 91 percent dose-dependent down-regulation of its target, clusterin, in prostate cancer. In the Phase I dose escalation trial, which was coordinated by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), investigators reported significant, dose-dependent inhibition of clusterin in prostate cancer patients compared to historical controls at several of the doses studied:

- 91 percent target reduction with a 640 mg dose of OGX-011
- 73 percent target reduction with a 480 mg dose of OGX-011
- 66 percent target reduction with a 320 mg dose of OGX-011
- 58 percent target reduction with a 160 mg dose of OGX-011

OGX-011 was well tolerated at the doses studied. The most frequently reported side effects were mild (grade 1 or 2) and included fevers, rigors, fatigue and transient elevations of AST and ALT, enzymes used to detect liver damage. No dose limiting toxicities were observed in the trial.

Based on tissue pharmacokinetic and optimal inhibition of the drug's target in prostate cancer cells and lymph nodes, 640 mg was recommended as the optimal dose for future Phase II studies of OGX-011. Trials of OGX-011 in combination with hormone and chemotherapy are planned to begin in 2004 in patients with prostate, breast and lung cancers.

A second Phase I study is in progress which is designed to determine recommended dose of OGX-011 in combination with TAXOTERE® in various solid tumors. This study is expected to be completed by the end of Q3, 2004. **(press release)**

OncoGenex and Isis established a drug development collaboration in 2001 to develop and commercialize OGX-011. This partnership combines OncoGenex's proprietary antisense position in secretory protein clusterin (sCLU) inhibitors with Isis' proprietary second-generation antisense chemistry called 2'-*O*-methoxyethyl. **(press release)**

Secretory Protein Clusterin (sCLU): The Target
OGX-011 is an inhibitor of sCLU, which is in the clusterin (CLU) family of proteins. sCLU acts as a cell-survival protein and is over-expressed in response to tumor killing strategies, such as chemotherapy, hormone ablation and radiation therapy. sCLU has been associated in preventing cell death in tumors, a function that may be related to its ability to clear cell debris after damage from tumor killing strategies. Inhibiting sCLU is intended to enhance the effects of traditional therapies in cancer treatment.

Prostate Cancer Facts:
According to the American Cancer Society, an estimated 230,110 new cases of prostate cancer will be diagnosed in the U.S. during 2004. An estimated 29,900 deaths from prostate cancer will occur this year, making the disease the second leading cause of cancer death in men. **(return to pipeline chart)**

ISIS 113715 is a second-generation antisense drug in Phase II development for the treatment of type 2 diabetes. The drug is currently in Phase II development with the goal of evaluating the drug's ability to regulate blood sugar levels in patients with type 2 diabetes.

Phase II development was initiated based on robust Phase I and preclinical data. In a Phase I study, ISIS 113715 enhanced insulin's ability to transport glucose, or blood sugar, into cells in normal volunteers. A primary characteristic of type 2 diabetes is inefficient use of glucose in spite of the availability of insulin. Correcting this defect is a goal in the management of the disease. ISIS 113715 did not cause hypoglycemia, or excessively low blood sugar, which is an adverse effect observed with many currently available treatments for type 2 diabetes. ISIS 113715 was well tolerated in the Phase I study.

In preclinical studies, ISIS 113715 demonstrated positive effects in five well-characterized and accepted animal models of diabetes. The drug normalized blood sugar levels in multiple rodent models and improved glucose tolerance in normal and obese monkeys. In addition, ISIS 113715 did not produce hypoglycemia or weight gain, a characteristic of many other type 2 diabetes treatments. ISIS 113715 has demonstrated consistent reduction of PTP-1B mRNA and protein levels in liver and fat, key tissues known to be important in the regulation of blood sugar levels.

PTP-1B: The Target

Diabetic patients are often prescribed insulin injections in order to regulate blood sugar. Insulin is a hormone secreted by the pancreas that directs cells to uptake sugar from the blood stream, thereby decreasing sugar concentration in the blood stream. PTP-1B is an enzyme that appears to reduce insulin's ability to regulate blood sugar levels. The inhibition of PTP-1B may allow the insulin receptors to stay active longer, allowing for more glucose uptake into cells and lowers levels in the blood stream.

Type 2 diabetes patients produce insulin, but their bodies do not react to the insulin, hence glucose is not absorbed into their cells and it is left in the blood stream. Over time, patients may become desensitized to insulin and will then require higher doses of insulin. The successful inhibition of PTP-1B may allow for the administration of lower doses of insulin to diabetic patients while still maintaining satisfactory blood sugar levels. **(press release)**

Type 2 Diabetes Facts:

According to the National Institutes of Diabetes and Digestive and Kidney Diseases, approximately 17 million Americans are affected by diabetes, a metabolic disease that affects the body's use of sugars. Type 2 diabetes, also known as adult-onset diabetes, accounts for 90-95% of all diagnosed diabetes cases. **(return to pipeline chart)**

ATL-1102 (ISIS 107248) is a second-generation antisense inhibitor of VLA-4, which is in development for multiple sclerosis (MS). Inhibition of VLA-4 has been shown to have positive effects in multiple animal models of inflammatory diseases, including MS.

Results of a dose-escalating Phase I study of ATL-1102 announced in June 2004 showed that 6 mg/kg/week of ATL-1102 appeared well-tolerated and has been selected as the proposed dose for Phase 2 development. A Phase 2 clinical trial is expected to begin in the second half of 2004.

The double-blind, randomized, dose-escalation, placebo-controlled Phase 1 study evaluated the pharmacokinetic and safety profile of ATL-1102. In 54 healthy volunteers, ATL-1102 was either delivered in an intravenous (IV) or subcutaneous (SQ) formulation. ATL-1102 was well-tolerated. The most frequently reported side effects included mild "flu-like" symptoms and occasional injection site reactions, which were generally mild and increased in incidence and severity with escalating dose levels, particularly at 12 and 18 mg/kg/week. The trial was conducted at the Charterhouse Clinical Research Unit of the Ravenscourt Park Hospital (formerly Stamford Hospital) in London. **(press release)**

Isis licensed ATL-1102 to Australian-based Antisense Therapeutics Limited (ATL) in 2001. Isis completed preclinical studies, and ATL is responsible for future clinical development, manufacturing and commercialization of the

compound.

VLA-4: The Target

ATL-1102 is an inhibitor of CD 49d, a sub-unit of VLA-4 (Very Late Antigen-4). In multiple sclerosis, white blood cells (leukocytes) are pulled into the central nervous system (CNS) from the blood. The inhibition of VLA-4 may prevent white blood cells from entering the CNS to stop the progression of MS. Inhibition of VLA-4 in animals has demonstrated positive effects in a number of inflammatory diseases such as MS.

Multiple Sclerosis Facts

According to the National Multiple Sclerosis Society, approximately one third of a million Americans acknowledge having MS and every week about 200 people are diagnosed. Worldwide, MS may affect 2 million individuals. **(return to pipeline chart)**

LY 2181308 (ISIS 23722) is the latest compound to emerge from Isis' cancer research program. This second-generation antisense drug was licensed to Eli Lilly and Company as a component of the companies cancer antisense drug discovery collaboration initiated in 2002. The oncology relationship builds on a broad, ongoing strategic alliance established to discover antisense drugs in the areas of inflamatory and metabolic diseases. **(press release)**

In April 2003, Isis achieved a significant milestone in the development of LY2181308. Lilly selected the compound for clinical development, and plans to begin Phase I studies in 2004. In preclinical studies, LY2181308 demonstrated activity in multiple *in vivo* models of cancer. **(press release)**

Survivin: The Target

LY2181308 targets survivin, a molecule that allows the survival of cells that would normally undergo programmed cell death or apoptosis. When cancer cells grow, they appear to need the help of survivin. The molecule is abundant in many types of cancers, including colon, brain, lung, skin and others, but nearly nonexistent in normal cells. **(return to pipeline chart)**

ISIS 301012 is the newest compound to be added to Isis' pipeline. It targets ApoB-100, which is a protein that plays a pivotal role in the production of low-density lipoprotein (LDL), the "bad" cholesterol.This molecule has been of great interest to the industry, yet has long been considered "undruggable" by traditional small molecule approaches.

The company initiated a Phase I study in late 2003. The double-blind, placebo-controlled, dose-escalation trial will enroll 40 healthy volunteers with borderline cholesterol. The goal of this trial is to assess the safety, tolerability and pharmacokinetic profile of ISIS 301012, and its ability to reduce several components of cholesterol that are important in the management and prevention of cardiovascular disease.

The company reported preliminary results of this Phase I study in August 2004 on the first 19 volunteers.

Preliminary Study Highlights:

* At Day 25, volunteers in the top three ISIS 301012 dose groups of 100 mg, 200 mg and 400 mg per dose demonstrated average decreases in lipids from baseline as follows:

* LDL reductions ranging from 27% (100 mg) to 44% (400 mg).
* VLDL reductions ranging from 14% (100 mg) to 38% (400 mg).

* Total cholesterol reductions ranging from 7% (100 mg) to 36% (400 mg).

* In addition, initial data from the three highest dose groups showed:

* Volunteers receiving ISIS 301012 experienced average reductions from baseline in apoB-100 protein levels in serum of up to 55%.
* ISIS 301012's onset of action was rapid, with reductions in apoB-100 and lipids observed at the first treatment evaluation time point of one week.
* Reductions in apoB-100 and associated decreases in LDL, VLDL and total cholesterol remained below baseline for two months or longer in a majority of volunteers. In contrast, placebo-treated volunteers demonstrated negligible apoB-100 or lipid changes during the study.
* ISIS 301012 improved cholesterol/high density lipid (HDL) and LDL/HDL ratios.
* To date, no treatment-related serious adverse events have been reported :
* The most commonly reported side effect was skin reactions at the site of subcutaneous injections, which did not interfere with continued treatment and were comparable in frequency and similar in degree to skin reactions observed with other subcutaneously administered drugs.
* In addition, minor increases in liver enzymes were observed in some volunteers. The increases correlated with reductions in cholesterol, were asymptomatic and similar in degree to those observed with other lipid regulating agents. **(press release)**

Isis plans to expeditiously advance the development of ISIS 301012.

Cardiovascular Disease Facts
Cardiovascular disease is the leading cause of death in the U.S., according to the National Institutes of Health. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Statistics from the American Heart Association state that nearly 105 million American adults have borderline high cholesterol and about 37 million American adults have levels of 240 or above. **(return to pipeline chart)**